REMARKS

The Claim Amendments

In order to advance prosecution and in response to the Office restriction of claim 1 between VEGF and VEGF receptor, Applicants have amended claim 1 with traverse to recite a method of locally administering to a tissue or cell a synthetic double stranded RNA comprising nucleotide sequence that is complementary to nucleotide sequence of a Vascular Endothelial Growth Factor receptor (VEGF receptor) encoding RNA comprising SEQ ID NO: 14 or a portion thereof. Support for the amendment is found on page 6, line 8. SEQ ID NO: 14 refers to the VEGF receptor 1 sequence of GenBank Accession No. NM_002019 (see page 6, line 8, referring to GenBank Accession No. NM_002019). In response to the Office restriction of claims 8 and 9 between VEGFR1 and VEGFR2, Applicants withdrew claim 9 without prejudice as being drawn to a nonelected invention. In this response, Applicant has canceled non-elected claim 9.

Amendments to the claims are made without prejudice and do not constitute amendments to overcome any prior art or other statutory rejections and are fully supported by the specification as filed. Additionally, these amendments are not an admission regarding the patentability of subject matter of the canceled or amended claims and should not be so construed. Applicant reserves the right to pursue the subject matter of the previously filed claims in this or in any other appropriate patent application. The amendments add no new matter and applicants respectfully request their entry.

Restriction Requirement

Claims 1, 8, and 9 are subject to restriction because they are not considered to be a proper genus/Markus and because they allegedly place an undue burden on the Office to search and examine more than one gene. As discussed above, Applicant has elected with traverse to prosecute the subject matter relating to VEGF receptor 1. Accordingly, claim 1 has been amended to reflect this and claim 9 has been canceled.

Priority

The Applicants acknowledge the Office's priority date of November 30, 2001.

35 U.S.C. § 112, Second Paragraph, Rejection

Claim 8 stands rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite because the term "VEGFR1" is not clearly defined. Claim 1 has been amended to recite the term "vascular endothelial growth factor receptor" as "(VEGF receptor)". Claim 8, which depends from claim 1, has been amended to recite VEGF receptor 1 as "VEGFR1". Support for the amendment can be found, *inter alia*, at page 5, lines 27-29. Given that the amendment obviates the rejection, Applicants respectfully request withdrawal of the 35 U.S.C. §112 second paragraph rejection.

35 U.S.C. § 112, First Paragraph, Rejections

Written description

Claims 1-8 and 10-26 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement, because the claims contain subject matter that was not described in the specification in such as way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Applicant respectfully traverses the rejection.

Under 35 U.S.C. § 112, first paragraph, all that is required to satisfy the written description requirement is that the specification describe the claimed invention in sufficient detail such that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306 (Fed. Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991); M.P.E.P § 2163(I). Possession is shown "by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention." M.P.E.P. §

2163.02 (citing *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir.1997)).

There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. M.P.E.P. § 2163(I)(A) (citing *In re Wertheim*, 541 F.2d 257, 263, 191 U.S.P.Q. 90, 97 (C.C.P.A. 1976)). Thus, a description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. *See, e.g., In re Marzocchi*, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971); M.P.E.P. § 2163.04. Therefore, the Office must have a reasonable basis to challenge the adequacy of the written description and has the initial burden of presenting, by a preponderance of the evidence, why a person skilled in the art would not recognize in an Applicant's disclosure a description of the invention defined by the claims. *See, e.g., In re Wertheim*, 191 U.S.P.Q. 90, 97 (C.C.P.A. 1976); M.P.E.P. § 2163.04.

Whether the specification shows that an applicant was in possession of the claimed invention is a factual determination. M.P.E.P. § 2163(I). Factors to be considered in determining whether there is sufficient evidence of possession include: (1) the level of skill and knowledge in the art; (2) partial structure; (3) physical and/or chemical properties; (4) functional characteristics alone or coupled with a known or disclosed correlation between structure and function; and (5) the method of making the claimed invention. *Id.* at (II)(A)(2)-(3)(a). Disclosure of *any* combination of such identifying characteristics that distinguish the claimed invention such that one skilled in the art would conclude that the applicant was in possession of the claimed species is sufficient. *Id*; *see Reagents of the Univ. of Calif. v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

The written description requirement can be met by a functional description of claimed materials, if it is coupled with a known or disclosed correlation between function and structure. *Enzo Biochem, Inc., v. Gen-Probe, Inc.*, 296 F.3d 1316, 63 U.S.P.Q.2d 1609 (Fed. Cir.2002).

Firstly, the Office Action asserts that the specification "does not teach a single double-stranded RNA molecule capable of RNA interference that is complementary to a nucleic acid molecule encoding a VEGF receptor" and that this "provides insufficient written description to support the genus encompassed by the claim." The Office Action concludes that "[w]ithout a disclosure of a single species of the genus, the skilled artisan cannot envision the detailed chemical structure of the encompassed nucleic acid molecule(s)" (Office Action at pages 8-9).

Second, the Office Action further asserts that "the invention encompasses nucleic acids that encode all forms of a VEGF receptor(s)" (see Office Action at page 9) and that "[t]here is no disclosure found in the specification or known in the art, at the time the instant invention was made that relates the structure of a double-stranded RNA molecule capable of RNA interference that is complementary to a nucleic acid molecule encoding a VEGF receptor as claimed in the instant invention" (see Office Action at page 9).

The Office Action concludes that "[t]he specification fails to describe the complete structure of a representative number of species of the claimed genus" (see Office Action at page 10) and that "[w]ithout a single disclosed species, one of skill in the art, at the time the instant invention was made, could not envision any double-stranded RNA molecule capable of RNA interference that is complementary to a nucleic acid molecule encoding a VEGF receptor...one of skill in the art would not be convinced that applicants were in possession of any double-stranded RNA molecule capable of RNA interference that is complementary to a nucleic acid molecule encoding a VEGF receptor that are heretofore undescribed" (see Office Action at page 11). The Office Action finally concludes that the claims do not satisfy the written description requirement because "the specification does not describe the claimed double-stranded VEGF receptor molecules for use in a method of locally administering to a cell or tissue in such full and concise terms so as to indicate that the applicant had possession of these nucleic acid molecules at the time of filing the application" (see Office Action at pages 11-12).

Contrary to the Office's assertions, the application as filed adequately describes the requisite identifying characteristics of the claimed invention such that one skilled in the art would be convinced that the Applicant had possession of the claimed invention. The instant specification provides an adequate description of the claimed invention by describing how to design, synthesize and test double stranded nucleic acid molecules that target VEGF receptors, including VEGFR1, and by providing specific examples of such double stranded nucleic acid sequences. As required by the written description requirement, the specification describes both structural and functional properties of the claimed invention. For example, the specification teaches that the double stranded nucleic acid is a double stranded RNA molecule where one strand of the RNA is complementary to RNA of a VEGFR1 gene (see page 8 lines 23-27). The specification further teaches the length of the individual double stranded nucleic acid strands (see page 9, lines 1-9), and various chemical modifications of the nucleic acid, including 2'-fluoro, 2'-O-methyl, and 2'-deoxy modifications (see page 38, lines 2-3 and 22-23). Importantly, the specification teaches the nucleotide sequence of the VEGFR1 target sequence (see page 6, line 8, referring to GenBank Accession No. NM_002019). In addition, the specification teaches how to identify target sites within the VEGFR1 target sequence (see for example page 33, line 27 to page 34, line 27 and U.S. Provisional Patent application NO. 60/393,796 at page 65, line 23 to page 68, line 12).

Additionally, the specification teaches one skilled in the art how to synthesize the claimed double stranded nucleic acid molecules (see for example page 34, line 28 to page 38, line 7), how to locally administer the claimed double stranded nucleic acid molecules (see for example page 46, line 20 to page 49, line 16), and how to evaluate the double stranded nucleic acid molecules in a mammalian cell or subject (see for example page 61, line 18 to page 62, line 8, and U.S. Provisional Patent application NO. 60/393,796 at page 68, line 20 to page 75, line 14 and data shown in Figure 3 demonstrating in vivo activity of a locally administered double stranded nucleic acid targeting VEGFR1). Thus, the specification teaches several of the factors to be considered in determining whether there is sufficient evidence of possession including the structure, physical and/or chemical properties, functional characteristics, and methods of making and using the claimed

invention. All of these teachings clearly demonstrate that Applicant had possession of the claimed invention.

With respect to the Office's first argument that the Applicant does not provide any examples of a double-stranded RNA molecule that is complementary to a nucleic acid molecule encoding a VEGF receptor, Applicant respectfully points out that the specification does discloses several specific examples of double stranded nucleic acid molecules that target VEGFR1. For example, SEQ ID NOS:1-33 of U.S. Provisional Patent application No. 60/393,796, which sequences are incorporated by reference in the instant application, are double stranded nucleic acid molecules that target VEGFR1. Thus, Applicant provides a representative number of species of the claimed genus sufficient to satisfy 35 U.S.C. § 112).

With respect to the Office's second argument, without acceding to the merits of the Office's argument, Claim 1 has been amended to recite a method of locally administering to a tissue or cell a synthetic double stranded RNA comprising nucleotide sequence that is complementary to nucleotide sequence of a Vascular Endothelial Growth Factor receptor (VEGF receptor) encoding RNA comprising SEQ ID NO: 14 or a portion thereof. As discussed above, the specification adequately describes the distinguishing identifying structural and functional characteristics of a double stranded nucleic acid complementary to VEGFR1 comprising SEQ ID NO: 14 and provides several examples of the nucleic acid molecules, all of which demonstrate that the Applicant had possession of the claimed invention at the time of filing. For the reasons stated above, Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. §112 rejection.

Enablement

Claims 1-8 and 10-26 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to describe the claimed subject matter in such a way as to enable one skilled in the art to make and/or use the invention. The Applicant respectfully traverses the rejection.

The specification as filed fully enables the claimed invention. The *Wands* factors typically considered by the Office in formulating the enablement rejection include the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention, and the quantity of experimentation necessary. All the applicant is required to show is that one skilled in the art would be able to make and use the claimed invention using the application as a guide. *In re Brandstadter*, 484 F.2d 1395, 1406-07, 179 USPQ 286, 294 (CCPA 1973). The showing provided by the applicant need not be conclusive but merely convincing to one skilled in the art (see MPEP 2164.05).

The Office argues that while the specification is enabling for a method of locally administering to a cell or tissue *in vitro* a double stranded RNA complementary to a nucleotide sequence of a VEGF receptor, it does not reasonably provide enablement for a method of locally administering to a cell or tissue *in vivo* (whole organism) (Office Action, page 12). Contrary to the Office's position that *in vivo* administration is not enabled, Applicant submits that the instant specification teaches appropriate methods of administration to cell and animal models and provides data that is reasonably predictive of administration *in vivo*. As established by the Federal Circuit, "if the art is such that a particular model is recognized as correlating to a specific condition then it should be accepted as correlating *unless the Examiner has evidence that the model does not correlate* (emphasis added)." MPEP 2164.02; *In re Brana*, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995). The various models taught in the specification are appropriate models that one skilled in the art would consider to be reasonably predictive of administration *in vivo*.

Furthermore, the specification teaches one skilled in the art how to make and use the double stranded nucleic acid for *in vivo* administration. The specification teaches one how to design (see for example pages 33-34), synthesize (see for example pages 34-38), and administer (see for example pages 46-55) double stranded nucleic acids that target VEGFR1. Furthermore, the specification teaches how to evaluate such double stranded nucleic acid molecules using *in vivo* animal models of angiogenesis (see for example pages 61-62 and U.S. Provisional Patent application NO. 60/393,796 at page 68, line 20

to page 75, line 14). The specification teaches that the double-stranded nucleic acids can be used to down regulate gene expression (page 33, lines 14-26) and also provides supporting evidence that inhibition of VEGFR1 expression using double stranded nucleic acids as claimed results in significant inhibition of angiogenesis *in vivo* (see for example pages 1-5 and 59-61 and U.S. Provisional Patent application NO. 60/393,796 at page 68, line 20 to page 75, line 14). Thus, the specification enables one of skill in the art to practice the claimed invention by describing how to design, synthesize, administer, and test double stranded nucleic acid molecules targeting VEGFR1 in vivo by providing specific examples of such double stranded nucleic acid molecules, and by demonstrating that the double stranded nucleic acid molecules inhibit angiogenesis.

As discussed above, the specification teaches methods of locally administering double stranded RNA molecules to a tissue or cell using appropriate models that are reasonably predictive of in vivo administration. Furthermore, using the teachings provided in the instant application, Applicant has actually shown that local administration of double stranded nucleic acid molecules targeting VEGFR1 gene expression can be used to inhibit angiogenesis *in vivo.* In U.S. Provisional Patent application NO. 60/393,796 at page 72, line 7 to page 75, line 14, which is incorporated by reference in the instant application, Applicant has demonstrated inhibition of angiogenesis as is presently claimed using a mouse model of ocular angiogenesis (data is shown in Figure 3). Also, in co-pending US Patent Application Nos.: 11/299,391, 10/844,076, and 10/962,898, Applicant demonstrates inhibition of ocular angiogenesis using double stranded nucleic acid molecules targeting VEGFR1 RNA in vitro and in vivo. As described in USSN 10/844,076 (published as US-2005-0171039-A1) and USSN 10/962,898 (published as US-2005-0222066), Applicant designed, synthesized, and tested several double stranded nucleic acid sequences that were evaluated for efficacy in cell culture and animal models.

As described in USSN 11/299,391, applicant describes Phase I clinical trial results obtained using Sirna-027, which is a modified siRNA molecule targeting VEGFR1 RNA. Sirna-027 is a modified siRNA in development as a potential therapeutic for the

pathological neovascularization common to ocular diseases such as age-related macular degeneration (AMD) and diabetic retinopathy. Sirna-027 is directed against vascular endothelial growth factor receptor 1 mRNA. VEGFR1 is the receptor in the VEGF pathway that can bind both VEGF and placental growth factor. Sirna-027 was efficacious in a mouse model of laser-induced choroidal neovascularization and in mice with ischemic retinopathy. Intravitreal or periocular injections of Sirna-027 resulted in significant reductions in ocular neovascularization in both mouse models, ranging from 32 to 66%, compared to treatment of the fellow eye with an inverted control siRNA (see co-pending application USSN 10/962,898, Example 10, pages 209-220). Ocular levels of VEGFR1 mRNA and protein were also reduced significantly. The methods and results were published in Shen *et al.,* 2005, *Gene Therapy*, 1-10. The safety, tolerability, clinical and biological activity of Sirna-027 was evaluated in an open-label, dose escalation Phase I trial in 25 patients with active choroidal neovascularization secondary to AMD. Single intravitreal injections of Sirna-027 (100 to 1200 μg) were safe and well tolerated. No ocular or systemic dose-limiting toxicities were observed. Eight weeks after the injection, all patients had stable or improved visual acuity. Reduction of central foveal thickness was observed by ocular coherence tomography in the majority of patients, suggesting biological activity of siRNA in a human (see co-pending application USSN 11/299,391, Example 9, pages 226-242).

Thus, employing the teachings in the instant application, Applicant has demonstrated a method of locally administering a double stranded RNA to a tissue or cell in vivo. Thus, the claims are enabled across the scope of the claims. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the 35 U.S.C. §112 rejection.

Conclusion

In view of the foregoing amendments and remarks, the applicant submits that the claims are in condition for allowance, which is respectfully solicited. If the examiner

believes a teleconference will advance prosecution, she is encouraged to contact the undersigned as indicated below.

Respectfully submitted,
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